

Amendment #2
Solicitation HHS-NIH-NIAID-BAA2017-1

AMENDMENT TWO (2)

OFFICE OF ACQUISITIONS

National Institute of Allergy and Infectious Diseases (NIAID)
5601 Fishers Lane, Room 3D32, MSC 9821
Rockville, MD 20852

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Issued By:

George W. Kennedy, Contracting Officer
Email: kennedyg@mail.nih.gov
Phone: 240-669-5170

Points of Contact:

Division of Allergy, Immunology, and Transplantation (DAIT)

Research Area 001: Adjuvant Development Program

Maribel Miranda, Contracting Officer
Phone: (240) 669-5139; E-mail: Maribel.Miranda@nih.gov

Research Area 002: Development of Radiation/Nuclear Medical Countermeasures;

Research Area 003: Development of Radiation/Nuclear Predictive Biomarkers and Biodosimetric Devices

Liem Nguyen, Contracting Officer
Phone: (240) 669-5144; E-mail: Liem.Nguyen@nih.gov

Division of Microbiology and Infectious Diseases (DMID)

Research Area 004: Development of Broad Spectrum Therapeutic Products for Biodefense, Anti-microbial Resistant Infections and Emerging Infectious Diseases;

Research Area 005: Advanced Development of Vaccine Candidates for Biodefense and Emerging Infectious Diseases

George Kennedy, Contracting Officer
Phone: (240) 669-5170; Email: kennedyg@mail.nih.gov

The hour and date specified for receipt of Offers remains unchanged.

Offerors must acknowledge receipt of the amendment by Amendment number(s) and date of the amendment. Include a statement of acknowledgement in your proposal submission. Failure of acknowledgement may result in rejection of your offer.

Except as provided herein, all terms and conditions of the solicitation remain unchanged and in full force and effect.

PURPOSE OF SOLICITATION AMENDMENT

The purpose of this amendment is to provide a revision to Section III, Research Area 003 of the subject solicitation, and respond to questions.

Accordingly, and with reference to the Solicitation Table of Contents, Solicitation HHS-NIH-NIAID-BAA2017-1, Section III, Subsection 2.B., **Research Area 003 – Development of Radiation/Nuclear Predictive Biomarkers and Biodosimetric Devices**, *Technical Approach*, pg. 20, ¶ 1, under the provision “This contract will provide funds to support the following activities:”, is revised to add the highlighted language as follows:

This contract will provide funds to support the following activities:

1. Non-clinical Research and Development, including:

- a. Validation of biomarkers to rapidly assess acute and/or delayed radiation-induced injuries to physiological systems/organs/tissues to inform triage and treatment decisions, and/or assessment of injury and recovery of specific organ/organ systems.
- b. Development of quantitative and accurate means to distinguish between non-irradiated and exposed (**≥ 2 Gy**) cohorts. Appropriate radiation quality, radiation doses and dose rate should be applied to animal models to obtain samples. Human clinical biosamples may be utilized if necessary to the study design.
- c. Reagent and assay development.
- d. Conduct of mechanism of action studies relevant to humans.
- e. Analysis of biomarker biokinetics (i.e., biomarker persists over a range of time permitting use in a radiation public health emergency – 30 minutes to days and weeks).
- f. Influence of confounders on the kinetics of the technique/biomarker (e.g., gender, age [pediatric and geriatric populations], smoking status, health status, current medications), type of radiation, partial body irradiation, other injuries (burn, trauma, wound).
- g. Biomarker studies in appropriate animal models, using relevant exposure conditions (radiation quality, dose, dose rate), and using minimally invasive biosamples (i.e., studies using fractionated radiation exposures, commonly used for clinical radiotherapy treatments would NOT be

appropriate, unless information gained would be directly applicable to an unintentional exposure scenario).

h. Clinical research testing *ex vivo* using human subject samples.

i. Efficacy studies in appropriate animal models, using relevant exposure conditions (radiation quality, dose, dose rate), and using easily available biosamples to test the device.

j. Development of a biodosimetry device, high-throughput, or other automated diagnostic systems for rapid radiation dose assessment following exposure, research that supports quantification of the radiation dose to the exposed individual to inform treatment strategies, and/or assessment of injury and recovery of specific organ/organ systems.

k. Conduct of IUO enabling studies for regulatory approval of an advanced device specific for the intended stage of response (triage or medical management), within a specified time-frame post-exposure (1-3 days post exposure for point-of-care, or 72 hours and beyond for medical management guidance), and defined biodosimetry biomarkers (*e.g.*, RNA, DNA, multiparametric, metabolomics).

l. Assessment of exposure to ionizing radiation in the range of 0 to 10 Gy, where the biomarker and/or device can distinguish between non-irradiated and exposed [$2 \text{ Gy} \pm 0.5 \text{ Gy}$] cohorts.

SOLICITATION QUESTIONS AND RESPONSES

This section provides the Government's responses to questions received regarding this solicitation. The responses are offered for information only and do not modify or become part of this solicitation. Additional amendments will be provided as needed to address further questions and their related responses. All potential offerors are advised to refer back to all previous amendments for additional questions and clarification.

GENERAL SOLICITATION QUESTIONS

Question 1: Is it allowable for me to contact the Program Officers for guidance?

Answer 1: No. This is a competitive solicitation for contract proposals, all communications must be submitted to the Contracting Officer points of contact listed in Section II of the solicitation.

Question 2: Is the Proposal Intent Response Form required to be submitted in advance of a proposal?

Answer 2: The Proposal Intent Response Form is desired for planning purposes, but is not required. An organization may submit a proposal without having first submitted notice of its intent to propose.

Question 3: Our proposed response to this solicitation may be substantially similar in nature to another application we submitted in response to a different solicitation. Do you have any potential concerns regarding scientific overlap?

Answer 3: If an offeror submits a Statement of Work, in response to the subject solicitation, contains technical approach considered to be overlapped with other projects/studies performed under another contract/grant issued by the government, during negotiations the offeror will be requested to remove or revise the scientific overlap proposed in the Statement of Work.

SPECIFIC RESEARCH AREA QUESTIONS

The Government's responses to questions received regarding this solicitation are as follows:

Division of Allergy, Immunology, and Transplantation (DAIT) **Research Area 001: Adjuvant Development Program**

Question 1: In development of a specific adjuvant, is it better to focus on one disease, or demonstrate the potential broader application of the adjuvant to multiple diseases?

Answer 1: Offerors are encouraged to combine their adjuvant with one (or more) vaccines expected to specifically benefit from their adjuvant. While the simultaneous development of more than one vaccine with the same adjuvant can de-risk the project, the offeror is responsible for ensuring that the proposed work can be accomplished within the budget constraints described in the BAA. Furthermore, the vaccines being developed must protect against pathogens relevant to human disease (e.g., the development of a veterinary vaccine will not be supported by this funding mechanism).

Question 2: Additional clarification is hereby provided in regards to the following statements:

“an adjuvant is defined as a single immunostimulatory compound or a combination of synergistic stimulatory compounds”

“Each proposal must focus on the development or further optimization of only one adjuvant candidate for one or more licensed or investigational vaccines”

“Optimization of only one adjuvant (for one or more vaccines) for enhanced safety and efficacy; this may include structural alterations or modifications to formulation or delivery”

- a) For combinations of stimulatory compounds, would the selection of a single lead combination through optimization with 2-4 lead adjuvants in various combinations and formulations be acceptable?**
- b) Please define the flexibility provided for optimization of an adjuvant (or combinations) through structural alterations. Would limited lead optimization (5-15 compounds) around a core adjuvant compound be acceptable?**

Answer 2: a) The Technical Approach Section of Research Area 001 – Adjuvant Development Program – of this Omnibus BAA states that “each proposal must focus on development or further optimization of only one adjuvant candidate”. For the purpose of this BAA, adjuvants are defined as “agent(s) added to or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target the specific immune response(s) to the antigen” (in Background section). Therefore, an adjuvant can consist of a single compound or a combination of compounds. The goal of each project must be the development of a single adjuvant (or single combination-adjuvant) for one or more human vaccines (licensed or investigational). Studies can be proposed to optimize the adjuvant:vaccine combination to assure the vaccine formulation is safe and efficacious. Optimization strategies, which may include modifications of the formulation or delivery, have to be focused on the adjuvant:vaccine combinations being pursued throughout the performance period of the contract project.

While the BAA excludes the screening for new adjuvants or the parallel development of several different adjuvants, it does not prohibit studies aimed at optimizing a combination adjuvant through

selection of the most appropriate formulation from a small number of functionally equivalent compounds, all of which must have previously shown to have vaccine-adjuvant activity (e.g., variants of agonists for a specific TLR). The scope of such studies should only include studies for selection of the final adjuvant formulation, and the majority of the proposed work must focus on the final combination adjuvant, as outlined in the Technical Objectives Section of Area 001.

- b) Optimization of the adjuvant used for a defined adjuvant:vaccine combination includes structural alterations to the adjuvant molecule(s) aimed at optimizing its activity. Since the BAA mandates “Optimization of only one adjuvant“, the offeror is required to select a defined lead candidate (single or combination adjuvant), which can be further optimized by evaluating structural variants of this lead compound.

Question 3: With regards to Research Area 001 (Adjuvant Development Program), would it be within the scope of the solicitation to investigate combinations of adjuvants for the purpose of improving efficacy, reducing toxicity, and/or reducing cost?

Answer 3: While each proposal must focus on the study of one adjuvant, for the purpose of this solicitation, an adjuvant is defined as a single immunostimulatory compound or a combination of synergistic stimulatory compounds. Thus, the development of a combination adjuvant is within the scope of the solicitation; however, the BAA prohibits the active discovery of new adjuvant combinations.

Question 4: Is NIAID specifically seeking proposals focused on any particular diseases such as influenza or NIAID Category A, B or C pathogens OR would proposals against ANY disease except HIV be responsive?

Answer 4: Adjuvant studies must focus on one or more non-HIV disease pathogen(s) relevant to human disease, where pathogens relevant to human disease are not limited to influenza or NIAID Category A, B, or C pathogens.

Question 5: Does NIAID require that the data demonstrating successful *in vivo* augmentation of vaccine efficacy be performed with the same vaccine as proposed or would proof of concept data of adjuvant efficacy/augmentation with one vaccine for one disease be sufficient to support development with a different vaccine for a different disease (assuming the mechanisms of augmentation were expected to be relevant to the mechanism of protection afforded by the second vaccine)?

Answer 5: The proposal must include documentation that the adjuvant safely augments the ability of a vaccine to protect against pathogen challenge in an *in vivo* animal model. The pathogen challenge or vaccine used for this documentation may be different than the vaccine or pathogen described in the Statement of Work.

Question 6: Would NIAID be interested in adjuvants that specifically supported dose sparing of existing vaccines for flu or biothreats?

Answer 6: The development of a novel adjuvant:vaccine combination is justified by the anticipated benefit the adjuvant provides to the vaccine. Examples of such benefits are: enhanced and/or prolonged efficacy of the vaccine, accelerated onset of protection, as well as dose sparing to stretch the vaccine supply without compromising vaccine efficacy.

Question 7: We previously developed an influenza vaccine in which the antigen is decorated with a TLR-agonist. Recently, we have identified a more effective method to decorate the antigen and have also improved the methodology involved in this process, This 2nd generation vaccine would be

tested in NHPs as well as in aged and neonatal mice. We also propose to apply the adjuvant platform to other viral vaccines. Are these studies within the scope of the BAA?

Answer 7: The BAA supports the development of novel adjuvant:vaccine combinations against pathogens which are relevant for human disease. The NIAID acknowledges the need for new vaccines particularly for special populations such as the elderly and newborns. Since the proposed adjuvant:vaccine combination had not previously been supported by the NIAID Adjuvant Development Program and the proposed modification of the adjuvant will result in a different vaccine-product, the proposed research is not affected by exclusion criteria 1 and 2 of this solicitation (BAA document p7). The BAA allows the development of vaccines against one or more (non-HIV) pathogens relevant to human disease, using the same adjuvant. All work on same adjuvant/different vaccine-combinations have to be geared towards the testing and further development of each adjuvant:vaccine combination and involve IND-enabling studies as described in the BAA.

Question 8: If I've obtained prior NIAID funding to develop a vaccine adjuvanted with a particular adjuvant, is it acceptable to submit an application to develop the same adjuvant for a vaccine targeted against the same pathogen but using a different antigen?

Answer 8: The BAA prohibits continued work on an adjuvant:vaccine combination that had been supported during the previous iteration of the program. However, it is acceptable to propose developing the same adjuvant with a unique vaccine targeting the same pathogen since this new adjuvant:vaccine combination is considered a new product by the U.S. Food and Drug Administration (FDA) and would require further development toward licensure for human use.

Question 9: If I've obtained prior NIAID funding to develop a vaccine adjuvanted with a particular adjuvant, is it acceptable to submit an application to develop the same adjuvant for a vaccine against a completely different pathogen?

Answer 9: The BAA prohibits continued work on an adjuvant:vaccine combination supported during the previous iteration of the program. However, it is acceptable to propose developing the same adjuvant with a vaccine against a different pathogen since this new adjuvant:vaccine combination is considered a new product by the U.S. Food and Drug Administration (FDA) and would require further development toward licensure for human use.

Question 10: Can you let me know what 'investigational vaccine' refers to? i.e. is it required for the vaccine to have already been clinically tested or can it be a preclinical vaccine under development?

Answer 10: In the context of this BAA, investigational vaccines are defined as experimental vaccines that have not been licensed for use in humans yet. Vaccines that are included in the NIAID Adjuvant Development program are not required to have previously been evaluated in clinical trials, but offerors will need to provide at least preclinical data that justify the further development of the adjuvant:vaccine combination. When proposing to use materials (adjuvants or vaccines) from a third party, please note Paragraph 8 in "(D) PROJECT MANAGEMENT" which states that documentation is required showing that the offeror has intellectual property protection and/or proprietary freedom to develop the proposed formulation.

Question 11: We have developed a liposome-based adjuvant technology that is flexible in that it can be easily manipulated to generate different immune response profiles depending on what components are included in the liposome. Would the liposome itself could be considered as the adjuvant? Could we propose to tailor it to a particular antigen by adding in different immunostimulatory molecules to achieve the desired immune response?

Answer 11: a) If the liposome itself has no inherent immunostimulatory activity (i.e., the development of a

liposomal carrier), then it would not be considered an adjuvant. However, the further development of a liposome paired with a defined immunostimulatory molecule or defined combination of immunostimulatory molecules would be responsive. The use of liposomes without adjuvant activity falls under activities described in TECHNICAL APPROACH/Product Development plan: “Evaluate formulation... of the adjuvant:vaccine”

- b) The initial testing of multiple immunostimulatory compounds with liposomes without adjuvant activity would not be supported through this solicitation, since such activity is considered screening, which is not permitted. Each individual proposal must only include the development or further optimization of a single adjuvant, with an adjuvant being defined - for the purpose of this solicitation - as a single immunostimulatory compound or a combination of synergistic stimulatory compounds.
- c) If the liposome has adjuvant activity itself, the initial testing with a limited number of immunostimulatory compounds is allowable as described in the answer to question 2a and would represent the selection of a combination adjuvant. However, only one liposome-coadjuvant combination may be further developed and optimized.

Question 12: We have been developing an adjuvant that can be used to amplify immune responses to antigens either alone or in combination with other immunostimulatory molecules. Would a proposal to further test and develop formulations of synthetic versions of an adjuvant to identify the most potent analog both alone and in combination with other immunostimulators be of interest?

Answer 12: Under this BAA, the *optimization* of an adjuvant *may include structural alterations* or modifications to formulation or delivery. While each proposal must focus on the study of one adjuvant, for the purpose of this solicitation, an adjuvant is defined as a single immunostimulatory compound or a combination of synergistic stimulatory compounds. Therefore, a single proposal could include the further testing and development of formulations of synthetic versions of an adjuvant to identify the most potent analog or the further testing and development of formulations of an adjuvant/immunostimulatory molecule combination, but a single proposal could not include both activities. The BAA prohibits the active screening and discovery of new adjuvants, such as the *de novo* synthesis of mimetics and screening of those novel mimetic/immunostimulatory compounds to identify potent combinations.

Question 13: We have a PI that is applying for Research Area 001 and would like for it to be a multiple PI proposal. I have reviewed the guidelines and could not find that this is disallowed but wanted to confirm before we submit.

Answer 13: Yes, multiple PI's may be proposed.

Division of Allergy, Immunology, and Transplantation (DAIT)

Research Area 002: Development of Radiation/Nuclear Medical Countermeasures

Question 1: The solicitation states “NIAID anticipates that one or two awards may be issued for a total cost of up to \$2 million for the non-severable base work across all contracts (direct and indirect costs combined), depending on the number of technically meritorious proposals, importance to the agency programs, and availability of funds.” Does this mean that NIAID will award \$2M total of combined direct and indirect cumulative across all awardees?

Answer 1: NIAID anticipates up to 2 awards to be issued as a result of the solicitation, for up to \$2 million across all contracts, on an annual basis; a total of \$6M for a 3-year period across all awards. The \$2M includes direct and indirect costs of all contracts issued under Research Area 2.

Question 2: Is this Research Area open to all business sectors?

Answer 2: For this Research Area the Prime contractor must be a US entity where the subcontractor(s) can be foreign.

Question 3: Is oral mucositis caused by radiation therapy a condition that would fall under the scope of the contract?

Answer 3: We are not focused on damage caused by radiation therapy but on the exposure after a mass casualty incident.

Question 4: Are there specific diseases that are higher or lower priority?

Answer 4: Heme, GI and Pulmonary ARS or DEARE are the highest priority.

Question 5: Are there specific animal models that the contract is most interested in seeing a compound being tested?

Answer 5: Not necessarily, as long as the animal model is appropriate for the testing of MCM in the intended syndrome.

Question 6: Do you have a particular concept for a product that is preferred (e.g., pill, topical cream, spray)? Are there any special restrictions on portability, storage, use, etc. that would lead to a product concept preference?

Answer 6: We prefer routes of administration and stability profiles that are suitable for mass casualty situations.

Question 7: Are there any sites in particular that are more important to treat locally (e.g., GI, skin) or do you prefer systemic treatment?

Answer 7: No, application is dependent on the syndrome and suitability for mass casualty situations.

Division of Allergy, Immunology, and Transplantation (DAIT)

Research Area 003: Development of Radiation/Nuclear Predictive Biomarkers and Biodosimetric Devices

Question 1: The solicitation states “NIAID anticipates that one or two awards may be issued for a total cost of up to \$2 million for the non-severable base work across all contracts (direct and indirect costs combined), depending on the number of technically meritorious proposals, importance to the agency programs, and availability of funds.” Does this mean that NIAID will award \$2M total of combined direct and indirect cumulative across all awardees?

Answer 1: NIAID anticipates up to 2 awards to be issued as a result of the solicitation, for up to \$2 million across all contracts, on an annual basis; a total of \$6M for a 3-year period across all awards. The \$2M includes direct and indirect costs of all contracts issued under Research Area 3.

Question 2: Is this Research Area open to all business sectors?

Answer 2: For this Research Area the Prime contractor must be a US entity where the subcontractor(s) can be foreign.

Question 3: Will propose a device that could discriminate between non-exposed samples (0.0 Gy) and samples exposed to a dose of radiation of ≥ 0.5 Gy be considered responsive?

Answer 3: Refer to the first section of this amendment, revising the language in subparagraphs 1.b. and 1.l. of the Technical Approach (page 20-22) to add:

This contract will provide funds to support the following activities:

1. Non-Clinical Research and Development, including:

b. Development of quantitative and accurate means to distinguish between non-irradiated and exposed (≥ 2 Gy) cohorts. Appropriate radiation quality, radiation doses and dose rate should be applied to animal models to obtain samples. Human clinical biosamples may be utilized if necessary to the study design.

l. Assessment of exposure to ionizing radiation in the range of 0 to 10 Gy, where the biomarker and/or device can distinguish between non-irradiated and exposed [$2 \text{ Gy} \pm 0.5 \text{ Gy}$] cohorts.

Division of Microbiology and Infectious Diseases (DMID),

Research Area 004: Development of Broad Spectrum Therapeutic Products for Biodefense, Anti-Microbial Resistant Infections and Emerging Infectious Diseases

Question 1: Are there limitations (e.g. corporate form, foreign/domestic) on who may propose to this solicitation?

Answer 1: This Broad Agency Announcement is being solicited as full and open; that is, any responsible offeror may submit a proposal for consideration.

Question 2: The solicitation states that the therapeutic must display activity against viruses classified as NIAID Category A, B, or C viral threat agents, but several families of viruses are also listed. Is the development of a broad-spectrum therapeutic against Category A broad Arenaviruses in response to this BAA?

Answer 2: Page 29 of the solicitation, Research Area 004, Section 2. Antiviral Broad-spectrum Therapeutics, states that a candidate antiviral therapeutic product must meet all of the criteria identified. Thus, an antiviral broad spectrum therapeutic that displays activity against Arenaviruses (part of the Category A viral pathogens under the NIAID Priority Pathogens List), must also display activity against infection caused by two or more viruses from the families identified in Section 2.b. to be considered responsive.

Question 3: What level of development does a broad-spectrum therapeutic product need to be in? (e.g. Beyond validation and mechanism determination.) Are animal experiments expected to have been performed or is it responsive to have animal work within the contract?

Answer 3: Page 28 of the solicitation, Research Area 004, Technical Objectives, states that lead candidates must show all of the following characteristics: -Demonstrated feasibility of manufacturing, -*In vitro* and *in vivo* evidence of efficacy, and -Sufficient characterization to allow the development of a draft target product profile.

Question 4: Would a proposal with animal model data for efficacy against Gram-negative infections, and in vitro data demonstrating activity against MDR clinical strains, satisfy criterion b on page 29 of the BAA? Is animal efficacy data required for the biodefense pathogens, or is the in vitro MIC data sufficient?

Answer 4: Page 28 of the solicitation, Research Area 004, Technical Objectives, states that lead candidates must show all of the following characteristics: -Demonstrated feasibility of manufacturing, -*In vitro* and *in vivo* evidence of efficacy, and -Sufficient characterization to allow the development of a draft target product profile.

This does not mean that *in vivo* animal efficacy data must be inclusive of all bacterial strains listed in subparagraph b.

Question 5: Regarding antiviral broad-spectrum therapeutics. Do proposals need a candidate that will be effective against multiple virus families (eg Flaviviruses and Filoviruses) or effective against multiple viruses within a single family (eg Zaire, Sudan and Marburg)?

Answer 5: The candidate broad-spectrum therapeutic antiviral shall have activity against more than one member of virus family or have activity against two or more virus species from more than one virus family, within the virus families listed in Sections 2a and 2b on page 29.

Question 6: Is a broad-spectrum candidate for an antiviral therapeutic considered only to be a single molecule or can it be a formulation comprising a cocktail of molecules (eg a cocktail of monoclonal antibodies)?

Answer 6: The BAA does not specify the number of molecules contained in the therapeutic candidate provided it is “A drug (synthetic or natural product) or a biological product (e.g. monoclonal antibodies, recombinant proteins) intended for use in the cure, mitigation, or treatment of two or more bacterial or viral pathogens”, on page 29.

Division of Microbiology and Infectious Diseases (DMID),

Research Area 005: Advanced Development of Vaccine Candidates for Biodefense and Emerging Infectious Diseases

Question 1: Are there limitations (e.g. corporate form, foreign/domestic) on who may propose to this Research Area?

Answer 1: This Broad Agency Announcement is being solicited as full and open; that is, any responsible offeror may submit a proposal for consideration.

Question 2: Are we permitted to submit more than one proposal for Research Area 005 (e.g. 2 separate proposals for vaccine candidates addressing different target pathogens)?

Answer 2: Offerors are not limited to the submission of one proposal.